PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
A61K 38/05, 38/06, C07K 5/00

A1

(11) International Publication Number: **WO 99/17790**

(43) International Publication Date: 15 April 1999 (15.04.99)

(21) International Application Number: PCT/US98/21055

(22) International Filing Date: 7 October 1998 (07.10.98)

(30) Priority Data:

60/061,309	7 October 1997 (07.10.97)	US
09/166,808	6 October 1998 (06.10.98)	US

(71) Applicant: CEPHALON INC. [US/US]; 145 Brandywine Parkway, West Chester, PA 19380 (US).

(72) Inventors: CHATTERJEE, Sankar; 228 Henley Road, Wynnewood, PA 19096 (US). MALLAMO, John, P.; 616 Font Road, Glenmoore, PA 19343 (US). BIHOVSKY, Ron; 804 Primrose Lane, Wynnewood, PA 19096 (US). WELLS, Gregory, J.; 818 Serpentine Drive, West Chester, PA 19382 (US).

(74) Agents: MILLER, Suzanne, E. et al.; Woodcock Washburn Kurtz Mackiewicz & Norris LLP, 46th floor, One Liberty Place, Philadelphia, PA 19103 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: PEPTIDE–CONTAINING α–KETOAMIDE CYSTEINE AND SERINE PROTEASE INHIBITORS

(57) Abstract

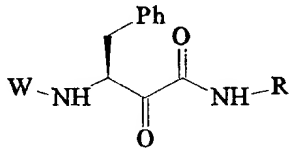
This invention relates to peptide–containing α–ketoamide inhibitors of cysteine and serine proteases, methods for making these compounds, and methods for using the same.

50	$CH_2CH_2N(CH_3)SO_2Ph$	(100%) **	C	645

Compounds listed inTable 4 were prepared by the general methods A-G described above.

Table 4

Inhibitory Activity of α- Ketoamides



Ex. No.	W	R	Calpain IC_{50} nM	MS (M+1)
51	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$-(3-(2-NH_2-thiazol-4-yl)Ph)	29	729
52	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$-(5-(3-formylphenyl)thiophene-2-yl)	5	741
53	Ms-D-Ser (Bn)	$CH_2CH_2NHC(=N\text{-}CN)OPh$	15	635
54	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-(Me_2NCH_2)phenyl)thiophene-2-yl)	12	770
55	Ms-D-Ser (Bn)	3-Boc-NH-cyclohexane	42	645
56	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-(morpholinoCH_2)phenyl)thiophene-2-yl)	18	812
57	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(4-(MorpholinoCH_2)Ph)	18	730
58	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-(N-Me-piperazinyl-CH_2)phenyl)thiophene-2-yl)	21	825
59	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-($HOCH_2$)phenyl)thiophene-2-yl) (2 diast)	35	765 (M+Na)

60	Ms-D-Ser (Bn)	$CH_2CH_2SO_2NHPh$	47	631
61	Ms-D-Ser (Bn)	$CH_2CH_2SO_2NH(4\text{-}CF_3Ph)$	32	699
62	Ms-D-Ser (Bn)	$(CH_2)_3SO_2NHPh$	18	645
63	Ms-D-Ser (Bn)	$(CH_2)_3SO_2NH(4\text{-}CF_3Ph)$	23	713
64	Ms-D-Ser (Bn)	6-ketopiperidin-3-yl	(33)*	545
65	Ms-D-Ser (Bn)	$CH_2CH_2N(Me)SO_2$-(5-(3-formylphenyl)thiophene-2-yl)	19	755
66	Ms-D-Thr (Bn)	$CH_2CH_2NHSO_2$(5-pyrid-2-ylthiophene-2-yl)	12	728
67	Ms-D-Ser (Bn)	-$N(Me)SO_2$-(5-isoxazol-3-yl-thiophene-2-yl)	21	718
68	Ms-(D,L)-Phenylgly	$CH_2CH_2NHSO_2$(5-pyrid-2-ylthiophene-2-yl)	21	670
69	Ms-(D,L)-Phenylgly	$CH_2CH_2NHSO_2Ph$	80	587
70	Ms-D-Thr (Bn)	$CH_2CH_2NHSO_2$(5-(3-(morpholinoCH_2)phenyl)thiophene-2-yl) (Mixture of diastereomers)	23	826
71	Ms-D-Phe	$CH_2CH_2NHSO_2$(5-pyrid-2-ylthiophene-2-yl)	18	684
72	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-Fluorophenyl)thiophene-2-yl) (Mixture of diastereomers)	18	731
73	Ms-D-Ser (Bn)	$(CH_2)_3SO_2NHOCH_3$	87	597 (M-1)
74	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$-(5-(3-Nitrophenyl)thiophene-2-yl) (Mixture of diastereomers)	15	758
75	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$-(5-(3-Methylphenyl)thiophene-2-yl) (Mixture of diastereomers)	36	727
76	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-(AcNH)phenyl)thiophene-2-yl) (Mixture of diastereomers)	11	792 (M+Na)

77	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-(CH_3CO)phenyl)thiophene-2-yl) (Mixture of diastereomers)	10	777 (M+Na)
78	Ms-D-Ser (Bn)	1-(4-(Morpholinomethyl)benzenesulfonyl)piperidin-4-yl) (Mixture of diastereomers)	48	770
79	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$((4-(CH_3COPh)piperazin-1-yl)CH_2Ph) (Mixture of diastereomers)	11	847
80	Ms-D-Ser (Bn)	$(CH_2)_3SO_2NH$-morpholin-4-yl	169	652 (M-1)
81	Ms-D-Ser (Bn)	$(CH_2)_3SO_2$-morpholin-4-yl	124	639
82	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$-(5-(4-Methoxyphenyl)thiophene-2-yl) (Mixture of diastereomers)	13	765 (M+Na)
83	Ms-D-Ser (Bn)	$CH_2CH_2CH_2$-Saccharin	48	657
84	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$((4-($PhCH_2$)piperazin-1-yl)CH_2Ph)	23	819
85	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$((4-(CH_3CO)piperazin-1-yl)CH_2Ph)	14	771
86	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$-(5-Me_2N-naphth-1-yl)	49	724
87	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$-benzothiophene-2-yl	23	687
88	Cbz-Leu-Leu	$CH_2CH_2NHSO_2$(5-pyrid-2-ylthiophene-2-yl)	33	819
89	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$((4-Pyrid-2-yl)piperazin-1-yl)CH_2Ph) (Mixture of diastereomers)	21	806
90	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$-(5-(4-formylphenyl)thiophene-2-yl)	17	741
91	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(4-(2-($MeOCH_2$)PyrrolidinylCH_2)Ph)	19	758

92	Ms-D-Ser (Bn)	$(CH_2)_5NHSO_2$(5-pyrid-2-ylthiophene-2-yl) (Mixture of diastereomers)	12	756
93	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(2-(morpholinoCH_2)phenyl)thiophene-2-yl)	40	812
94	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(4-(morpholinoCH_2)phenyl)thiophene-2-yl)	22	812
95	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-(piperidinylCH_2)phenyl)thiophene-2-yl)	30	810
96	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(2-acetamido-4-methylthiazol-5-yl)	23	709
97	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(1-phenylsulfonylpiperidin-4-yl)	32	671
98	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$-(5-(2-formylphenyl)thiophene-2-yl)	24	741
99	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$((CH_3O)CH_3NCH_2Ph) (Mixture of diastereomers)	21	704
100	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(4-ethylpiperazin-1-yl)CH_2Ph) (Mixture of diastereomers)	21	756
101	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-(Et_2NCH_2)phenyl)thiophene-2-yl)	22	798
102	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-(Cyclohexyl(Me)NCH_2)phenyl)thiophene-2-yl)	36	838
103	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-(pyrrolidinylCH_2)phenyl)thiophene-2-yl)	24	796
104	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-cyanophenyl)thiophene-2-yl)	10	738
105	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(4-(4-acetamidophenoxy)CH_2Ph)	14	816 (M+Na)
106	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-(azetidinylCH_2)phenyl)thiophene-2-yl)	44	782

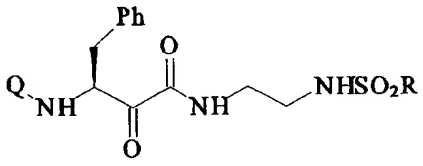
107	Ms-D-Ser (Bn)	1-(5-pyridin-2-ylthiophene-2-yl-SO_2)Piperidin-4-yl) (Mixture of diastereomers)	23	754
108	Ms-D-Ser (Bn)	$CONHCH_2CH_2NHSO_2$(5-(3-(N-ethyl-N-methylaminomethyl)phenyl)thiophene-2-yl)	10	784
109	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-(bis(2-methoxyethyl)aminomethyl)phenyl)thiophene-2-yl)	22	858
110	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-cyanophenyl)thiophene-2-yl) (Mixture of diastereomers)	11	738
111	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(4-(3-pyrrolin-1-yl)CH_2Ph) (Mixture of diastereomers)	73	712
112	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$((4-(CH_3SO_2)piperazin-1-yl)CH_2Ph)	37	807
113	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$((4-pyrimid-2-yl)piperazin-1-yl)CH_2Ph	24	807
114	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-(thiomorpholinoCH_2)phenyl)thiophene-2-yl)	33	828
115	Ms-D-Ser (Bn)	$CH_2CH_2NHSO_2$(5-(3-(4-ketopiperidinylCH_2)phenyl)thiophenc-2-yl)	16	824
116	Ms-L-Ser (Bn)	$CH_2CH_2NHSO_2$Ph	100	631

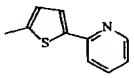
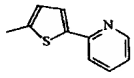
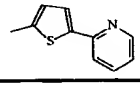
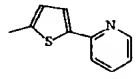
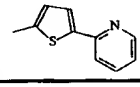
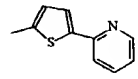
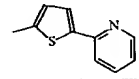
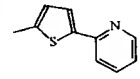
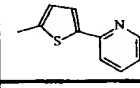
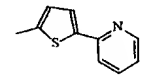
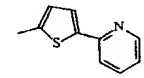
*Percent inhibition @ 0.1 μM

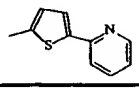
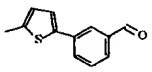
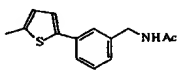
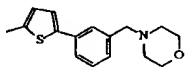
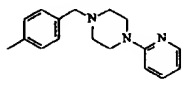
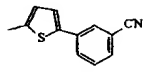
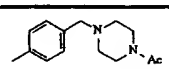
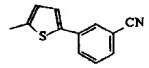
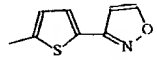
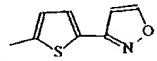
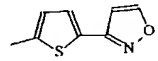
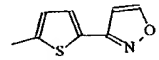
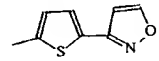
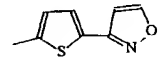
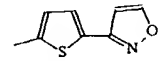
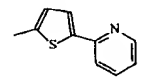
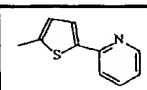
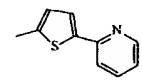
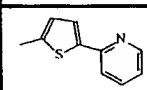
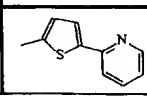
Ms = methylsulfonyl

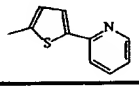
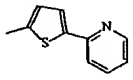
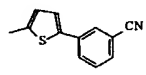
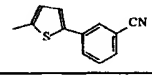
Table 5

Inhibitory Activity of Achiral P_2 Mimetic α-Ketoamides



Ex. No.	Q	R	Calpain IC_{50} nM	Synthesis Method	MS $(M+1)^-$
117	Benzoyl		800	A	563
118	2,6-Dichlorobenzoyl		36	A	631, 633
119	2,6-Dichloro-3-methylbenzoyl		61	A	645
120	2,6-Difluorobenzoyl		20	A	599
121	2,4,6-Trifluorobenzoyl		85	A	618
122	2,3,4,5,6-Pentafluoro-benzoyl		28	A	653
123	3,4-Methylenedioxy-benzoyl		>1000	A	607
124	2,5-Dichlorobenzoyl		68	A	631, 633
125	2-Chloro-5-methoxybenzoyl		65	A	627
126	3,5-bis(trifluoro-methyl)benzoyl		600	A	699
127	2,6-Dimethylbenzoyl		178	A	591

128	2,6-Dichloronicotinoyl		80	A	634, 636
129	2,6-Dichlorobenzoyl		21	A	658, 660
130	2,6-Dichlorobenzoyl		20	A	687, 689
131	2,6-Dichlorobenzoyl		29	A	729, 731
132	2,6-Dichlorobenzoyl		83	A	723, 725
133	2,6-Dichlorobenzoyl		11	A	655, 657
134	2,6-Dichlorobenzoyl		100	A	688, 690
135	2,6-Difluorobenzoyl		22	A	645 (M+Na)
136	2,6-Difluorobenzoyl		62	A	611 (M+Na)
137	2,6-Diethylbenzoyl		145	A	631 (M+Na)
138	2,6-Dimethoxybenzoyl		4000	A	613
139	2-Isopropylbenzoyl		168	A	595
140	2-Chloro-6-fluorobenzoyl		58	A	605
141	2-Fluoro-6-trifluoro-methylbenzoyl		58	A	639
142	2,3,4,5,6-Pentafluoro-benzoyl		32	A	643
143	2-Methylpropanoyl		1500	A	529
144	3-Methylbutanoyl		590	A	543
145	4-Methylpentanoyl		29	A	557
146	3-Cyclopentylpropanoyl		1000	A	583
147	E-3-Hexenoyl		1000	A	555

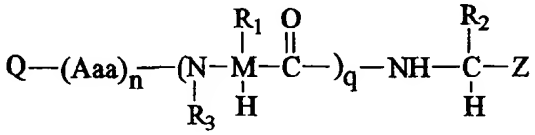
148	4-Phenylpentanoyl		87	A	641 (M+Na)
149	4-Phenylbutanoyl		1500	A	627 (M+Na)
150	4-Methylpentanoyl		15	A	603 (M+Na)
151	3-Cyclopentylpropanoyl		420	A	607

As those skilled in the art will appreciate, numerous changes and modifications may be made to the preferred embodiments of the invention without departing from the spirit of the invention. It is intended that all such variations fall within the scope of the invention.

It is intended that each of the patents, applications, and printed publications mentioned in this specification be hereby incorporated by reference in their entirety.

What is claimed is:

1. A compound having the Formula I:



I

wherein:

Q has the formula G-B-$(CHR^4)_v$ where R^4 is independently H or alkyl having from 1 to 4 carbons;

v is 0, 1, or 2;

B is selected from the group consisting of C(=O), OC(=O), $S(=O)_m$, CH_2, a bond, $NR^5C(=O)$, $S(=O)_m$-A-C(=O), and C(=O)-A-C(=O), where R^5 is H or lower alkyl;

m is 0, 1, or 2;

A is lower alkylene or cycloalkylene, optionally substituted with one or more halogen atoms, aryl, or heteroaryl groups;

M is a carbon atom;

G is selected from the group consisting of H, a blocking group, lower alkyl, lower alkenyl, aryl having from about 6 to about 14 carbons, heterocyclyl having from about 5 to about 14 ring atoms, heterocycloalkyl having from about 5 to about 14 ring atoms, arylalkyl having from about 7 to about 15 carbons, heteroarylalkyl, and arylheteroalkyl wherein the aryl portion can be unfused or fused with the heteroalkyl ring, said alkyl, aryl, heterocyclyl, heterocycloalkyl, arylalkyl, heteroarylalkyl, and arylheteroalkyl groups being optionally substituted with one or more J groups;

J is selected from the group consisting of halogen, CN, nitro, lower alkyl, cycloalkyl, heterocycloalkyl, heteroalkyl, halogenated alkyl, aryloxyalkyl, alkylthio, alkylsulfonyl, aryl, heteroaryl, arylalkyl, arylalkyloxy,

arylsulfonyl, heteroarylsulfonyl, alkoxycarbonyl, alkoxyalkyl, acyl, alkoxy, hydroxy, carboxy, hydroxyalkyl, amino, alkylamino, and aminoalkyl, said amino group or said amino group of said aminoalkyl or alkylamino group being optionally substituted with an acyl group, an alkoxy group, or with 1 to 3 aryl, lower alkyl, cycloalkyl, or alkoxyalkyl groups; and said aryl, heteroaryl, heterocycloalkyl, and heteroalkyl groups being further optionally substituted by a J group;

each Aaa is independently an amino acid which optionally contains one or more blocking groups;

n is 0, 1, 2, or 3;

R^1 and R^2 are independently selected from the group consisting of H, alkyl having from one to about 6 carbons, arylalkyl having from about 7 to about 15 carbons, heteroalkyl in which the ring contains from about 5 to about 14 ring atoms, heteroarylalkyl in which the heteroaryl ring contains from about 5 to about 14 ring atoms, alkoxyalkyl, a side chain of a naturally occurring amino acid in the R or S configuration, and $(CH_2)_pNH$-L, said alkyl, arylalkyl, heteroalkyl, heteroarylalkyl, and alkoxyalkyl groups being optionally substituted with one or more J groups;

p is 0, 1, 2, or 3;

L is selected from the group consisting of alkoxycarbonyl having from 2 to about 7 carbons, arylalkoxycarbonyl in which the arylalkoxy group contains about 7 to about 15 carbons, and $S(=O)_2R^6$;

R^6 is selected from the group consisting of lower alkyl, and aryl having from about 6 to about 14 carbons;

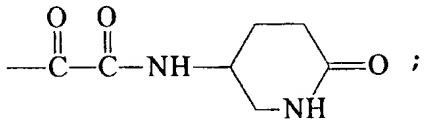
R^3 is selected from the group consisting of H, alkyl having from one to about 6 carbons, arylalkyl having from about 7 to about 15 carbons, heteroalkyl in which the ring contains from about 5 to about 14 ring atoms,

heteroarylalkyl in which the heteroaryl ring contains from about 5 to about 14 ring atoms, alkoxyalkyl, a side chain of a naturally occurring amino acid in the R or S configuration, $(CH_2)_pNH$-L, $C(=O)R^7$, $S(=O)_2R^7$, a blocking group, and when combined with the carbon atom to which R^1 is attached an alkylene group having from 2 to 5 carbons, said alkylene group being optionally substituted with a group selected from the group consisting of aryl, azide, CN, a protected amino group, and OSO_2-aryl, said alkyl, arylalkyl, heteroalkyl, heteroarylalkyl, and alkoxyalkyl groups being optionally substituted with one or more J groups;

R^7 is selected from the group consisting of aryl having from about 6 to about 14 carbons, heteroaryl having from about 5 to about 14 ring atoms, arylalkyl having from about 7 to about 15 carbons, alkyl having from 1 to about 10 carbons, said aryl, heteroaryl, arylalkyl and alkyl groups being optionally substituted with one or more J groups, heteroalkyl having from 2 to about 7 carbons, alkoxy having from about 1 to about 10 carbons, and amino optionally substituted with 1 or more alkyl groups;

q is 0 or 1;

Z is selected from the group consisting of $C(=O)C(=O)NH$-X-A^1-K and

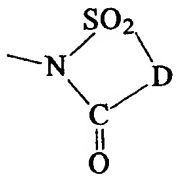


;

X is a bond or -O-;

A^1 is the same as A;

K is selected from the group consisting of $N(R^{10})Y$,


, and $SO_2N(R^8)(R^{10})$;

D is a fused aryl or heteroaryl group;

R^{11} is selected from the group consising of alkoxy, aryloxy, and NHR^{12};

R^{12} is selected from the group consisting of H, alkyl, aryl, and heteroaryl, said alkyl, aryl or heteroaryl groups being optionally substituted with one or more J groups;

Y is selected from the group consisting of SO_2R^8, $C(=O)NHR^9$, $C(=S)NHR^9$, $C(=NCN)R^{11}$, $C(=NC(=O)NHR^{10})R^{11}$, and CO_2R^8;

R^8 is selected from the group consisting of alkyl, alkoxy, aryl, and heterocyclyl, said alkyl, alkoxy, aryl, or heterocyclyl groups being optionally substituted with one or more J groups;

R^9 is selected from the group consisting of H, alkyl, aryl, and heteroaryl, said alkyl, aryl, or heteroaryl groups being optionally substituted with one or more J groups;

or an R^9 alkyl group may be combined with an A^1 alkylene group to form a N-containing heterocyclic 5- or 6-membered ring;

R^{10} is selected from the group consisting of H and lower alkyl;

or in the moiety $SO_2N(R^8)R^{10}$, R^8 and R^{10} may be combined together with the N atom to which they are attached to form a N-containing heterocyclic 5- or 6-membered ring;

or where A^1 is an alkylene group, and K is $N(R^{10})Y$ wherein R^{10} is alkyl, said R^{10} alkyl group may be combined

with said A^1 alkylene group to form a N-containing heterocyclic 5- or 6- membered ring;
or a pharmaceutically acceptable salt thereof.

2. The compound of claim 1 wherein n and v are each 0, q is 1, B is a bond, and G is H.

3. The compound of claim 1 wherein R^1 is the sidechain of a naturally occurring amino acid.

4. The compound of claim 1 wherein R^3 is $-S(=O)_2R^7$.

5. The compound of claim 1 wherein R^2 is benzyl or alkoxyalkyl.

6. The compound of claim 1 wherein X is a bond, and Y is SO_2R^8.

7. The compound of claim 1 wherein A^1 is $-CH_2-CH_2-$, $-CH_2-CH(CH_3)-$, or $-(CH_3)CH-CH_2-$.

8. The compound of claim 1 wherein R^1 is a serine sidechain, which is optionally capped with a benzyl group.

9. The compound of claim 8 wherein M is a carbon atom in the D configuration.

10. The compound of claim 1 wherein R^2 is benzyl, R^7 is methyl, and R^8 is substituted phenyl, unsubstituted phenyl, substituted heteroaryl, or unsubstituted heteroaryl.

11. The compound of claim 1 wherein R^8 is aryl, aryl substituted with amino, aryl substituted with

heterocyclomethyl, heteroaryl, alkyl substituted with heteroaryl, or heteroaryl substituted with alkylthio, haloalkyl, alkyl, phenylsulfonyl, halogen, aminophenyl, amino, or dialkylaminoalkyl.

12. The compound of claim 1 wherein n and v are each 0, q is 1, R^1 is the side chain of an amino acid in the D- or L-configuration, R^3 is $S(=O)_2R^7$, G is H, B is a bond, R^2 is benzyl or alkoxyalkyl, X is a bond, and Y is SO_2R^8.

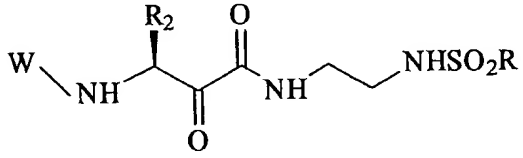
13. The compound of claim 1 wherein A^1 is CH_2CH_2, $CH_2CH(CH_3)$, or $(CH_3)CHCH_2$.

14. The compound of claim 1 wherein R^1 is a serine side chain in the D-configuration in which the hydroxyl group is capped with benzyl, R^2 is benzyl, R^7 is methyl, and R^8 is substituted or unsubstituted phenyl or substituted or unsubstituted heteroaryl.

15. The compound of claim 1 wherein R_1-R_4, B, G, Aaa, X, A^1, Y, n, q and v are selected in accordance with Tables 2 and 3.

16. The compound of claim 1 wherein R_1-R_4, B, G, Aaa, X, A^1, Y, n, q and v are each independently selected from the group of substituents shown in Tables 2 and 3.

17. The compound of claim 1 having the Formula:

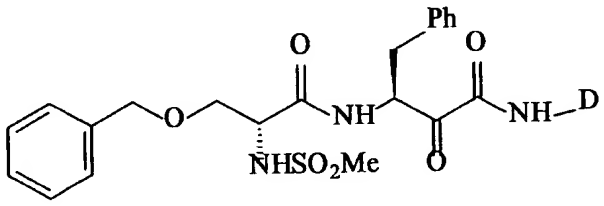


wherein:

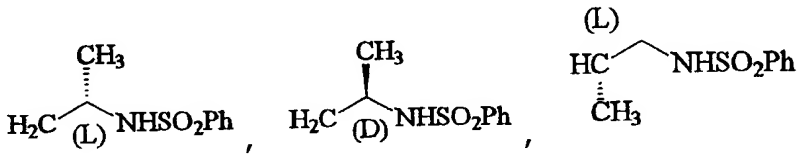
W, R_2 and R are independently selected from the group of substituents shown in Table 2.

18. The compound of claim 17 wherein W, R_2 and R are selected in accordance with Table 2.

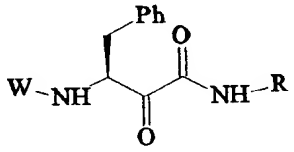
19. The compound of claim 1 having the Formula:



wherein D is $CH_2CH_2N(CH_3)SO_2Ph$ or has one of the formulas:



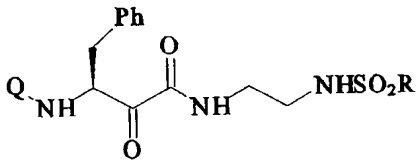
20. The compound of claim 1 having the formula:



wherein W and R are independently selected from the group of substituents shown in Table 4.

21. The compound of claim 20 wherein W and R are selected in accordance with Table 4.

22. The compound of claim 1 having the Formula:



wherein Q and R are independently selected from the group of substituents shown in Table 5.

23. The compound of claim 22 wherein Q and R are selected in accordance with Table 5.

24. The compound of claim 1 wherein n, v and q are each 0; B is (C=O); and G is phenyl or lower alkyl, said phenyl or lower alkyl groups being optionally substituted with one or more J groups.

25. A composition for inhibiting a serine protease or a cysteine protease comprising a compound of claim 1 and a pharmaceutically acceptable carrier.

26. A method for inhibiting a serine protease or a cysteine protease comprising contacting a protease selected from the group consisting of serine proteases and cysteine proteases with an inhibitory amount of a compound of claim 1.